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Letter to the Editor

Serial Examination of 20,248 Newborns: Correlations Between Drug Exposure and Major Malformations

To the Editor:

It is with great interest that we read the Letter to the Editor by Martínez-Frías [1997] regarding our publication on correlations between drug exposure and major malformations. We are pleased to continue this scientific discussion and to have the opportunity to comment on the statements made by the authors as follows:

1. In the described population-based study, we investigated 20,248 newborn fetuses and infants. There was *no selected* control group, because we investigated the entire population. A total of 1,472 births with major malformations (cases) and 9,682 births *without major and minor* malformations (controls) were analyzed. This implies that 9,094 children had minor malformations (mild errors of morphogenesis [MEM]). The MEM cases (e.g., preauricular tags, preauricular sinus, synophrys, hemangioma, single umbilical artery) classified by Méhes [1988] and Merlob [1994] were excluded from the control group, because associations between MEM and drug exposure cannot be excluded.

2. The study design of the Mainz model is a population-based case-control study. From 1990 to 1994, we used a standardized procedure to examine 20,248 newborns (19,945 livebirths, 121 stillbirths, 182 spontaneous abortions >15th week of gestation as well as induced abortions) in the region of Mainz. Therefore, the prevalence rates are calculated directly and systematic deviations as well as biases are absent [Hennekens and Buring, 1987, pp 135–136]. Confounding factors were tested for *drug intake* and maternal disease (P value = 0.292), maternal age > 35, (P = 0.939), race (P = 0.961), urban/rural differences (P = 0.697), alcohol abuse (P = 0.93), smoking (P = 0.557), and another 21 anamnestic factors. The P values of these associations were far from statistically significant. The indepth testing for confounding factors would not have been sufficient to reach statistical significance, due to the small number of exposed cases.

3. Testing associations between insulin treatment and major malformations are not identical to the testing of maternal nongestational diabetes mellitus and major malformations. The study includes all mothers receiving insulin during one of the two predetermined periods of therapy. This also includes mothers with gestational diabetes and malformed children. Therefore, the combination of major malformations and the administration of insulin cannot be completely disregarded, but most authors view diabetes mellitus and not insulin as a risk factor.

4. We reported no statistically significant associations between chromosome aberrations and drugs used during gestation.

5. The odds ratios of the reported 13 statistically significant results range between 2.9 and 11.6. All other data shown are marked as, "Not reaching statistical significance."

6. One of the aims of our publication was to present an overview of the most relevant data obtained by our *first* analyses. In this basic study we established 30 drug categories to obtain a sufficient number of exposed cases to determine the relevant categories for further indepth investigations (e.g., antiallergics, bronchodilators).

We completely agree with the statement that a careful handling of crude data is required. However, results obtained by a population-based study reflect a certain degree of reliability. The results of the study reflect a cautious attitude toward maternal drug use during the first trimester of gestation. Most drugs have *not* been shown to be associated with an increased teratogenic risk. However, the drug categories with the calculated significant risks require further research.

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